REMARKS

Claims 1-11 and 13-30 are pending in this application and have been rejected by the Examiner. Claim 12 has previously been canceled. Claims 15-30 are withdrawn. Claims 1-11 and 13-14 have been amended to clarify the claims and to remove the non-elected invention. It is believed no new matter has been added.

Restriction Requirement

Previously, the Examiner restricted the claims thirteen ways for lack of unity of invention, arguing that U.S. Patent 4,639,436 (Junge et al.) anticipates the claimed compounds of Group I. *Office Action* dated 7/29/2008, p. 4. Applicants respectfully disagree. It is well established that to be anticipatory, the prior art must disclose, whether explicitly or implicitly, every element of the claim. Junge et al. discloses desoxynojirimycin compounds and does not disclose a compound having the same stereochemical configuration as the claimed invention. As such, Junge et al. does not anticipate the claimed invention. In fact, all of the claims of the invention contain the general inventive concept involving a compound having a structural formula and stereochemistry as disclosed in Formula (I), i.e., a (2S, 3R, 4R, 5S) configuration, which is novel and non-obvious over the art and therefore meets the unity of invention standard. Applicants respectfully request the Examiner to reconsider and withdraw the finality of the restriction requirement.

Rejection under 35 *U.S.C.* § 112, Second Paragraph

The Examiner rejected claims 1-10 and 13-14 for being indefinite. The Examiner argued that the structural formula of the compounds of the current invention uses the dotted ("----") and the wedged ("▬") configurations, which allegedly denotes the up and down configuration from the ring, rather than the well recognized "*R*" and "*S*" configuration and therefore does not limit the claimed compounds to a specific stereochemistry. *Office Action* dated 12/11/2009, p. 2-3. The Examiner, therefore, concluded that the claims are without stereo limitations and as such are indefinite.

Applicants respectfully disagree. MPEP 2173.05(t) provides that "[c]laims to chemical compounds and compositions containing chemical compounds often use formulas that depict the chemical structure of the compound. These structures should not be considered indefinite nor speculative in the absence of evidence that the assigned formula is in error." Here, the Examiner did not argue that the structure is in error, but that the structure did not specify the stereo limitation. To this point, MPEP 2173.02 provides that "a claim term . . . is not indefinite if the meaning of the claim term is discernible." *Id.* citing *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004) (holding that the disputed claim term which was not defined or used in the specification was discernible and hence not indefinite because "the components of the term have well recognized meanings, which allow the reader to infer the meaning of the entire phrase with reasonable confidence"). Here, it is well known in the chemical art that the use of a solid wedge depicts a bond projecting from the paper towards the reader, while the dash wedge (or dash line) depicts a bond projecting from the paper away the reader. *See* "*Organic Chemistry*" Francis A. Carey, p. 28 (2nd Edition, McGraw-Hill, Inc., 1992). It is also well known that the absolute stereochemistry (R) or (S) of a compound may be determined by using the well-known Cahn-Ingold-Prelog two step procedure wherein (1) the four substituents on the chiral carbon are prioritized using the well-known Sequence Rule and (2) the configuration (R) or (S) is assigned based on the clockwise or counter-clockwise direction (respectively) of the atoms when the four substituents are observed with the lowest priority atom directed away from the reader and going from the highest priority substituent to the lowest priority substituent (i.e., in the order of decreasing precedence of the three highest-ranked substituents). *See* "*Organic Chemistry*" Robert Thornton Morrison and Robert Neilson Boyd, p. 138-141 (5th Edition Allyn and Bacon, Inc. 1987); *See also* "*Organic Chemistry*" Francis A. Carey, p. 269, Table 7.1 (2nd Edition, McGraw-Hill, Inc. 1992). Specifically, Francis A Carey states:

> Compounds in which a stereogenic center is part of a ring are handled in an analogous fashion. To determine, for example, whether the configuration of (+)-4-methylcyclohexene is *R* or *S*, treat the right- and left-hand paths around the ring as if they were independent substituents. Orienting the molecule with the hydrogen directed away from us, we see that the order of decreasing sequence rule priority is clockwise. The absolute configuration is *R*.

"*Organic Chemistry*" Francis A. Carey, p. 271 (2nd Edition, McGraw-Hill, Inc. 1992) (Emphasis added). Therefore, given the structural formula (I) with the solid wedge and dash line to denote which substituent is pointing up or down, one skilled will be able to discern with reasonable confidence the absolute stereochemistry of the compounds of the claimed invention (i.e., (2S, 3R, 4R, 5S)). As such, Applicants respectfully submit that the rejection under Section 112, Second Paragraph is improper. Withdrawal of the rejections under this section is earnestly requested.

Rejection under 35 *U.S.C.* § 112, First Paragraph

The Examiner rejected claims 1-11 and 13-14 for failing to comply with the enablement requirement, arguing that the specification does not provide "sufficient information as to what kind of modification of the drug functional groups to provide an inactive prodrug which will be released into the active form in vivo." *Office Action* dated 12/8/2008, p. 3. Applicants respectfully disagree. Page 5, paragraph [0105] of the published specification (2006/0058349) provides that "[s]uitable prodrugs of the compounds of formula (I) include, but are not limited to, pharmaceutically acceptable esters such as C_{1-6} alkyl esters." As such, the specification enables one skilled in the art to make and use C_{1-6} alkyl esters of formula (I) as a prodrug without undue experimentation. In view of these comments, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under Section 112, First Paragraph.

Rejection under 35 *U.S.C.* § 102(b)

The Examiner rejected claims 1-11 and 13-14 for being anticipated by Boeshagen et al. CA 113:126581; Ezure et al. CA 116:236093, RN 141206-38-4; Broek et al. CA 119:96007, RN 149302-52-3, RN 149302-53-4; Berg et al. RN 8117-43-3; Kurihara et al. CA 114:185939 RN 1333342-47-9, under 35 *U.S.C.* § 102(b) based on the conclusion that the claimed compounds do not contain any stereo limitation. *Office Action* dated 12/11/2008, p. 4. As argued in the Indefiniteness sections above, the solid wedge and dash (wedge/line) configuration is well understood and commonly used in the chemical art. By looking at the structural depiction of Formula (I), the stereo limitation of the compounds of the invention is apparent to one skilled in the art. As such, the claims require the compounds to have a specific stereochemistry (i.e., (2S, 3R, 4R, 5S)) and not without stereo limitation as concluded by the Examiner.

Boeschagen et al., CA 113:126581; Broek et al., CA 119:96007; Kurihara et al., CA 114:185939 and Berg et al., CA 96:117597 (the search results cited by the Examiner) all disclose compounds having a (2R, 3R, 4R, 5S) configuration, and Ezure et al., CA 116:236093 (the search results cited by the Examiner) discloses compounds having a (2R, 3S, 4R, 5S) configuration, all of which differ from the (2S, 3R, 4R, 5S) configuration of the claimed invention. It is well established that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Because none of these compounds have the stereochemical configuration as the claimed invention, they fail to anticipate the claims. For reasons stated above, reconsideration and withdrawal of the rejections under Section 102 is respectfully requested.

Rejection under 35 *U.S.C.* § 103

The Examiner rejected Claims 1-11 and 13-14 under 35 *U.S.C.* § 103(a) as allegedly being obvious over U.S. 5,051,407 ('407) as '407 allegedly discloses an anticipatory compound (CA 113:126581). The Examiner specifically pointed to a compound having a (2R, 3R, 4R, 5S) configuration wherein the ring nitrogen atom is substituted with an alkylphenyl group wherein said phenyl group is further substituted by R. *Office Action* dated 12/11/2008, p. 5. The Examiner argued that the difference between the prior art species compound and the claimed species compound is the substitution on the phenyl ring and that there is nothing unobvious about picking and choosing among the many alternatives choices of substituents such as nitro, cyano, amino, etc. delineated and exemplified in the prior art.

The Examiner also argued that the claimed invention is unpatentable over Jacob, U.S. 6,225,325 (Jacob et al.) in view of Greene. The examiner argued that Jacob et al. generically discloses 1,5-dideoxy-1,5-imino glucitol or galactiol compounds which inhibit glucosylceramide synthesis, that the reference exemplifies an instance wherein Ar1 is unsubstituted or methyl substituted and teaches that the protected hydroxy group is an alternative choice for the exemplified methyl. As the Greene reference discloses that the protected hydroxy includes benzyl protection, i.e., a benzyloxy moiety, the Examiner concluded that the claimed invention is obvious.

Applicants respectfully disagree. The substitution on the ring nitrogen is not the only difference between the claimed compounds and the prior art compounds. The solid wedge and dotted line notation used in the structural formula (I) of the claimed invention is well-recognized in the art. In looking at formula (I) of the invention, one skilled in the art will immediately recognize the stereo limitation of the claims. The Examiner admitted in the section on provisional obviousness-type double patenting rejection that the difference between the currently claimed compounds and copending Application No. 10/522,207 and 10/586,188 is the stereo-arrangement of the hydroxymethyl and the triol groups. The Examiner may not interpret the claims broader when considering them in view of the prior art for obviousness rejections, but narrower when considering them for double patenting purposes. As it is clear to one skilled in the art that the claims require compound of formula (I) to have a specific stereochemistry, Applicants respectfully submit that the prior art also does not teach the compounds of the invention.

The '407 reference, Column 1, lines 10-40 discloses a compound which is a desoxynojirimycin derivative while Boeschagen et al., CA 113:126581 (the search result) cited by the Examiner discloses compounds having (2R, 3R, 4R, 5S) configuration. All of these compounds have a different stereochemical configuration from the (2S, 3R, 4R, 5S) configuration of the claimed invention. Similarly, Jacob et al. discloses D-glucitol (i.e., DNJ) and galactitol compound (i.e., DGJ), both of which have different stereochemical configuration compared to the claimed compounds. Nothing in the '407 reference and in Jacob et al. reference suggests a reason for modifying their compounds to the (2S, 3R, 4R, 5S) compound of the invention. The Federal Circuit has held that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure.'." *Takeda Chemical Industries, LTD. v. Alpharma PTY., LTD.*, 492 F.3d 1350, 1356 (Fed Cir 2007). The Federal Circuit reaffirmed this holding in a recent case, stating that "post-KSR, a prima facie case of obviousness for a chemical compound still, in general begins with the reasoned identification of a lead compound" *Eisai Co. v. Dr. Reddy's Lab.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

With respect to the obviousness of enantiomers in view of the prior art, the Federal Circuit has also held that the dextrorotatory enantiomer of methyl alpha- 5(4,5,6,7-tetrahydro(3,2-c)

thienopyridyl)(2-chlorophenyl)-acetate, which possesses "all of the favorable antiplatelet activity but with no significant neurotoxicity" is unobvious over the known levorotarory enantiomer, which possesses "no antiplatelet activity but virtually all of the neurotoxicity". *Sanofi- Synthelabo v. Apotex*, WL 5191848, *4 (Fed. Cir. Dec. 12, 2008). Here, the prior art discloses DNJ and DGJ while the compounds of the claimed invention have a different stereochemical configuration. As the stereochemistry of a compound is intimately related to its biological activity, particularly in carbohydrate chemistry, the difference between the prior art compounds and the currently claimed compounds is neither trivial nor predictable. In fact, an article published in 2003 (after the priority date of the current application) by Butters et al. "Therapeutic Applications of Imino Sugars in Lysosomal Storage Disorders", *Current Topics in Medicinal Chemistry* (2003) 3:561-674, shows that the activities of different imino sugars are unpredictable. For instance, Table 1 of Butters et al. shows that deoxynojirimycin (DNJ) derivatives are not only up to 10 times less potent against ceramide-specific glucosyltransferase than its stereoisomer deoxygalactojirimycin (DGJ), but also significantly more active against α-glucosidase I, which α-glucosidase activity is known to cause undesirable side effects. *Id.* Alternatively, DGJ is more active for ceramide-specific glucosyltransferase activity and significantly more selective over α-glucosidase and than DNJ. These results show that changing the stereochemistry of a compound can dramatically affect its therapeutic activity and toxicity.

A similar pattern of unpredictable activity can also be seen in Kato et al., *J. Med. Chem.* (2005) 48:2036-2044, which publication is not prior art to the current application as it was published in 2004, after Applicants' PCT filing on July 17, 2003[1], yet relevant to the point that changing the stereochemistry of a compound may drastically change its biological activities. Tables 3 of the Kato article shows that the dextrorotarory enantiomer of deoxynojirimycin (D-DNJ) is active against human α- and β-glucosidase, but not active against human α- or β-mannosidase, α- or β-galactosidase, and α-fucosidase. L-DNJ, on the other hand, is not active

[1] Kato et al. was published on the Web on September 18, 2004. The current application is a national phase application under 35 U.S.C. 371 of PCT/GB2003/003244, which PCT application was filed on July 17, 2003, claiming priority back to July 17, 2002. PCT Article 11(3) provides that "...an international filing date shall have the effect of a regular national application in each designated State as of the international filing date, which date shall be considered to be the actual filing date in each designated State". As such, the effective filing date of the current application is July 17, 2003 and Kato et al. is not available as prior art.

against any of the human enzymes listed. D-*allo*-DNJ is not active against any of the listed human enzymes, but the L-*allo*-DNJ is active against human α-mannosidase. Similarly, D-*ido*-DNJ is active against human β-glucosidase and α-galactosidase, but L-*ido*-DNJ (which has the same configuration as the currently claimed compounds) is not active against any of the enzymes listed in the article. Applicants therefore respectfully submit that even with hindsight, it is difficult to rationalize the inhibitory activities of the various enantiomers of imino sugar compounds, let alone predict the activity of an enantiomer against a particular enzyme.

Given the unpredictability of activities of sugar and sugar mimetic compounds, one skilled in the art would not expect that all of the stereoisomers are active against a certain enzyme and therefore would not be motivated modify the prior art compounds and still have an expectation of success. Accordingly, disclosure of the DNJ and DGJ in the '407 patent does not render obvious the compounds of the invention. For the reasons stated herewith, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. 103(a).

Provisional Obviousness Type Double Patenting Rejection

The Examiner rejected Claims 1-11 and 13-14 on the ground that the claims of the present invention are allegedly unpatenable over the claims of copending Application No. 10/522,207 (hereinafter "the '207 Application) or 10/586,188 (hereinafter "the '188 Application) in view of U.S. Patent No. 5,051,407, U.S. Patent No. 7,256,005 ('005) and Kato et al. as being barred by the non-statutory obviousness-type double patenting. The Examiner argued that the only difference between the co-pending claims and the instant claims is the stereo arrangement of the hydroxymethyl and the triol groups and that the '407 and '005 reference teach that variations of the stereo structure of the piperidine core would not affect the activity. In addition, the Examiner argued that Kato et al. shows that "all enantiomers are biologically active while some may be more active or selective than others against specific enzymes." *Office Action* dated 12/11/2008, p. 6.

Applicants respectfully disagree. As discussed earlier, Kato et al., while not prior art to the current application, shows that biological activities of imino sugars are unpredictable (see arguments above). Even with hindsight, it is not explicable as to why one enantiomer is active against one enzyme and not another, let alone predicting the therapeutic activity and selectivity of

the enantiomers. Kato et al. actually supports Applicants' contention that the current invention is unobvious.

As discussed in the obviousness rejection section above, the '407 patent does not disclose the (2S, 3R, 4R, 5S) compound nor does the reference suggest a reason to modify their compounds to the compounds of the current invention. Although U.S. Patent 7,256,005 ('005) discloses a compound having the same configuration as the claimed compounds, Applicants note that this reference, to the extent that the Examiner relies on the disclosure of the arylalkyl substituted (2S, 3R, 4R, 5S) compound, is also not prior art to the invention. MPEP 2106.03 provides that "subject matter relied upon in the rejection must be disclosed in the earlier-filed application in compliance with 35 U.S.C. 112, first paragraph, in order to give that subject matter the benefit of the earlier filing date under 35 U.S.C. 102(e)." Here, the '005 patent was filed on September 23, 2003, after the current invention's effective filing date of July 17, 2003 and therefore may qualify as a 102(e) prior art. The '005 patent claims priority to three provisional applications and a PCT application (PCT/US00/21732). Even though the earliest priority date of the '005 patent is August 10, 1999, the (2S, 3R, 4R, 5S) arylalkyl substituted hydroxymethyl-piperidinetriol compound was not disclosed in Provisional application number 60/198,621 (filed April 20, 2000), provisional application number 60/148,101 (filed August 10, 1999) and PCT/US00/21732 (filed August 10, 2000). Rather, these applications focused on long alkyl chain derivatives of, among others, hydroxymethyl-piperidinetriol, e.g., C_{8-16}alkyl, particularly C_9alkyl, as antiviral agents, particularly exemplifying N-nonyl DNJ, DGJ and altro-DNJ. The arylalkyl substituted hydroxymethyl-piperidinetriol subject matter and the compound having the (2S, 3R, 4R, 5S) configuration was not introduced until the filing of provisional application number 60/412,560 on September 23, 2002. As the subject matter of the '005 patent relied on by the Examiner to reject the current claimed invention (i.e., arylalkyl substituted (2S, 3R, 4R, 5S) compounds) is not disclosed in the earlier priority applications, such subject matter does not afford the earlier priority dates. The current application, on the other hand, claims priority back to July 17, 2002, which predates provisional application 60/412,560. As such, the '005 patent, to the extent that the Examiner relied on the arylalkyl substituted (2S, 3R, 4R, 5S) hydroxymethyl-piperidinetriol subject matter, is not prior art to the claimed invention.

The remaining issue therefore is whether the disclosure of the long chain N-alkylated nitrogen containing compounds in the '005 patent such as N-nonyl-DNJ, N-nonyl-DGJ and N-nonyl-altrostatin, which all have different stereochemical configuration than the claimed compounds, render the claims to the arylalkyl substituted (2S, 3R, 4R, 5S) hydroxymethyl-piperidinetriol obvious. Again, Applicants argue they do not due to the unpredictability activity of imino sugars as seen in Kato et al. and Butters et al. Although the priority applications of the '005 patent discloses that various short-chain DNJ and DGJ (e.g., N-butyl DNJ and N-butyl DGJ) may have α-glucosidase and glycolipid synthesis inhibitory activities, they nevertheless do not provide any reason or motivation for one skilled in the art to modify these compounds so as to go from one enantiomer to another, particularly to the (2S, 3R, 4R, 5S) compound of the current invention. In fact, these references teach away from the claimed invention. For instance, WO 01/10429 (PCT/US00/21732) and U.S. Provisional Appl. No. 60/198,621 (both of which are priority applications of the '005 patent), disclose the following:

> [t]he nitrogen-containing virus-inhibiting compound can be administered to a cell or an individual affected by a virus. The compound can inhibit morphogenesis of the virus, or it can treat the individual . . . For example, the N-nonyl, N-decyl, N-3-oxa-nonyl, N-3-oxa-decyl, N-7-oxa-nonyl, N-7-oxa-decyl compounds are antiviral. The antiviral activity is substantially unrelated to the remaining functionalities of the compound . . .
>
> . . . Long chain N-alkyl compounds are agents that exhibit an inhibitory effect on viral expression. While certain short chain N-alkyl derivatives of imino sugars (e.g., N-butyl DNJ) are potent inhibitors of the N-linked oligosaccharide processing enzymes, such as α-glucosidase I and α-glucosidase II . . . Some long chain N-alkyl compounds of the invention may exhibit substantially little or no inhibition of a glycosidase enzyme, especially in comparison with N-butyl DNJ or N-nonyl DNJ. . . . For example, the nitrogen-containing virus-inhibiting compound can have an IC_{50} of about 10μM or less, preferably 3μM or less, for the inhibition of BVDV or another virus, but the same compounds may exhibit little activity against glycosidases or inhibition of glycolipid synthesis.

WO 01/10429, p. 12, lines 26-30, p. 13, lines 15-26 (*emphasis added)*; *Id.* at p. 25, Table 2; *See also* U.S. Prov. Appl. No. 60/198,621, p.11, lines 10-15 and p. 12, lines 1-12. As such, these applications claimed a broad class of nitrogen-containing virus-inhibiting compound which includes an N-C_{8-16}alkyl group. In reading this, one skilled in the art would conclude that the

activity is substantially unrelated to the hydroxy-piperidinyltriol core and that a shorter alkyl chain substitution would be desirable for glycolipid synthesis inhibitors rather the long, bulky arylalkyl groups as claimed in the current invention. This teaching would therefore discourage a skilled artisan from modifying the nitrogen-containing compounds of the '005 patent to produce the arylalkyl substituted (2S, 3R, 4R, 5S) compounds of the current invention and expect them to have GCS inhibitory activities. As such, the '005 patent teaches away from the invention and therefore does not render the currently claimed invention obvious over the claims of the co-pending applications. In light of the comments herewith, Applicants respectfully request withdrawal of the provisional obviousness type double-patenting rejections of claims 1-11 and 13-14.

In the event that the Examiner maintains the rejection, Applicants note that the later filed case ('188 Application) has not even been substantively examined yet, let alone issued as a patent nor have the claims been allowed in this case nor in the '207 case. As none of these applications have allowable claims, Applicants respectfully submit that the obviousness-type double patenting rejection is premature and respectfully requested that this rejection be addressed upon allowance of claims in at least one of the applications.

9. CONCLUSION

In summary, compounds of different stereochemistry, particularly sugars and sugar mimetics, may have completely different binding and/or biological activities as can be seen in Kato et al. and Butters et al. The teaching of one enantiomer as being biologically active would deter rather than motivate one skilled in the art to synthesize the other enantiomer, as there is no reason to expect the other compound to have the same activity, selectivity, or toxicity profile. Therefore, Appellants respectfully request that rejections of the pending claims be withdrawn.

As this response is filed within three months from the mailing date of the Non-final Office Action dated December 11, 2008, which response is due March 11, 2009, it is believed no fee is required. Should this be incorrect, the Commissioner is authorized to charge any additional fees, or credit any overpayment, to deposit account No. 50-4255.

Respectfully submitted,

Date March 11, 2009

By _____

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